REMARKS

Claims 1-31, 34 and 36-65 are pending in the application. Claims 1-26, 34, 37 and 41-65 are withdrawn. Claims 27-31, 36 and 38-40 are under examination and stand rejected.

Claims 27-29 and 39 have been amended and claims 30 and 40 have been canceled without prejudice or disclaimer. Support for the amendments can be found throughout the specification and the claims as originally filed. Therefore, the amendments add no new matter. Applicants respectfully request entry of the claim amendments and reconsideration based on the following remarks.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 27-31, 36 and 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Claim 27

The Office asserts that the preamble of claim 27 recites a method of guiding decisions, while the body of the claim does not recite positive steps for guiding nor does the body of the claim provide any correlation to guiding or how guiding is provided. Further, the Office asserts that it is unclear how the presence of the auto antibody guides therapeutic decisions for the subject. Office Action at page 3.

Without acquiescing to the Office's assertions but for the expedient prosecution of the present application, claim 27 has been amended. Support for the amendment can be found, e.g., in paragraph [0066] of the specification. As described in the specification, therapeutic decisions are possible based on the determination that a specific therapeutic inactivating component, such as an auto antibody, is present. *See* specification at paragraph [0066]. For example, the specification discloses that the level or concentration of a therapeutic agent administered may be altered based on

the presence and/or level of such a therapeutic inactivating component. *See id.* Therefore, no new matter has been added.

The amended claim 27 recites step c) as "altering level or concentration of said therapeutic administration of said natural substance to said subject based on the level of said auto antibody in step b)." Therefore, step c) qualifies as a positive step for guiding therapeutic decisions for a subject afflicted with an auto antibody for a natural substance. A person skilled in the art would find enough guidance in the language of amended claim 27 to alter the level or concentration of the natural substance based on the level of auto antibody in the subject.

Claim 27 is further amended to address the antecedent basis issue raised by the Office. Support for the amendment can be found in claim 27 as originally filed.

Claim 28

The Office asserts that there is insufficient antecedent basis for the recitations of "the medical condition" and "the underlying symptomology" in claim 28. Office Action at page 4.

Claim 28 has been amended to address the issue. Support for the amendment can be found in claim 28 as originally filed.

Claim 29

The Office asserts that it is unclear how drugs which are produced from different substances and are not found naturally are considered to be a "natural substance." Office Action at page 4.

Claim 29 has been amended to address the issue. Support for the amendment can be found, *inter alia*, in the specification at paragraph [0022], and in claim 28 as originally filed.

Claim 30

The Office asserts that claim 30 appears to contradict claim 27. Office Action at page 4.

Claim 30 has been canceled without prejudice or disclaimer. Therefore, this rejection becomes moot.

Claim 39

The Office asserts that there is no definition provided for the phrase "low molecular weight label" and that the recitation "low" is a relative term which renders the claim indefinite. Office Action at page 4.

Without acquiescing to the Office's assertions but for the expedient prosecution of the present application, claim 39 has been amended to incorporate the limitations found in the original claim 40 in regard to the molecular weight of the "low molecular weight label." Support for the amendment can be found in claims 39 and 40 as originally filed.

Further, the specification exemplifies what is included in the phrase "low molecular weight label," e.g., at paragraph [0032]. The specification states: "Frequently, the low molecular weight label comprises a radioactive label, e.g., Iodine-125, or a chemiluminescent label, e.g., luminol, although other low molecular weight labels are contemplated." Specification at paragraph [0032].

Claim 40

The Office asserts that claim 40 is vague and indefinite because of the recitation "capable of binding." Office Action at page 4.

Claim 40 has been canceled without prejudice or disclaimer. Therefore, this rejection becomes moot.

Applicants respectfully submit that the claims, as amended, are clear and definite. Accordingly, applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 27, 28, 30 and 36 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Lollar (U.S. 2005/0079584). Applicants respectfully traverse this rejection.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131.

Claim 30 has been canceled without prejudice or disclaimer. Therefore, Applicants address this rejection in regard to claims 27, 28 and 36 only.

The Office alleges that the recitation "basing therapeutic decisions to initiate, terminate, or adjust the level of therapeutic administration of dais natural substance to said subject on the presence of said auto antibody" recites an interpretive "basing therapeutic decisions" clause that is a non-manipulative mental step and does not inform the mechanics of how to guide or make decisions based on the presence of the auto antibodies. *See* Office Action at page 6. The Office further alleges that the clause does not recite any additional active method steps, but simply state a characterization or conclusion of the results of those steps. *See id.*

As discussed in detail above, claim 27 has been amended. The amended claim 27 recites step c) as "altering level or concentration of said therapeutic administration of said natural substance to said subject based on the level of said auto antibody in step b)." Applicants respectfully submit that the "altering level or concentration" clause in the amended claim 27 provides the mechanism of how to make and implement decisions based on the level of the auto antibodies and thus constitutes an additional active method step.

Lollar teaches isolated, purified, hybrid factor VIII molecules and fragments thereof with coagulant activity. *See* Lollar at paragraph [0016]. Lollar fails to disclose altering level or concentration of a therapeutic administration of a natural substance to a subject based on the level of an auto antibody. The Office asserts that Lollar discloses that the amount of the antibody in the test sample can be used to assist in the selection of medical therapies. *See* Office Action at pages 5-6. This is distinguishable from the "altering level or concentration" clause in the amended claim 27, because the reference provides no further disclosure of what "selection of medical therapies" means, its ordinary meaning appears to be "selecting among various medical therapies." A closer reading of paragraph [0038] of Lollar does not provide any additional information because the passage is directed to the diagnostic assays that may be used to detect and/or quantify the amount of antibodies against factor VIII. This does not inherently or expressly disclose the method of claim 27—the standard for inherent disclosure is met only if the missing claim limitation would necessarily be present in the reference's disclosure, which is not the case here. *See* MPEP § 2112. Thus Lollar does not teach each and every element of the claimed method recited in claim 27.

Because claims 28 and 36 are dependent on claim 27, the above remarks are applicable to claims 28 and 36 as well. Further, Lollar does not disclose the auto antibody is specific for a receptor involved in a biological pathway affected by the natural substance, as recited in claim 36.

Therefore, the Office does not make a *prima facie* case of anticipation because Lollar fails the strict identity standard for anticipation. Accordingly, the applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Conti-Fine in View of Lollar

Claims 27, 28 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Conti-Fine (U.S. 6,759,385) in view of Lollar. The office asserts that Conti-Fine discloses methods of detecting antibodies specific for an endogenous antigen and the administration of

endogenous protein or derivatives of the protein to a subject. Office Action at page 7. The Office further asserts that Conti-Fine discloses assessing antibodies produced as a result of the administration of the protein or its derivative and making decisions on therapeutic administration. *Id.* The Office states that Lollar discloses a method for determining if a patient comprises inhibitory antibodies to hybrid factor VIII, treating the patient with factor VIII, obtaining sample from the patient and assessing the sample for the presence of the antibodies, detecting antibodies with an ELISA or radioimmunoassay, etc. The Office concludes that it would have been obvious to one of skill in the art at the time the invention was made to incorporate ELISA or radioimmunoassay into the method of Conti-Fine. Office Action at page 8. Applicants respectfully traverse this rejection.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court in a recent case, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Intl Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). To make a prima facie case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* The initial burden to make a prima facie case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993).

Claim 30 has been canceled without prejudice or disclaimer. Therefore, Applicants address this rejection in regard to claims 27 and 28 only.

As discussed above, Lollar does not teach or suggest all the limitations of the presently claimed invention because Lollar fails to disclose altering level or concentration of a therapeutic administration of a natural substance to a subject based on the level of an auto antibody. Conti-Fine does not teach or suggest this limitation either. As the Office acknowledges, the combination of Conti-Fine and Lollar "teaches obtaining a sample from the subject and testing the sample for the presence of auto antibodies specific for the natural substance." Office Action at page 9.

Furthermore, the withdrawal of the previous rejection under 35 U.S.C. § 102(e) based on Conti-Fine acknowledges that Conti-Fine does not disclose all limitations of the presently claimed invention.

Accordingly, the Office has failed to establish a *prima facie* case of obviousness because combining Conti-Fine and Collar does not teach or suggest all limitations of the presently claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conti-Fine in View of Lollar Further in View of Bunn

Claims 29 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Conti-Fine in view of Lollar and further in view of Bunn (346 N. ENGL. J. MED. 522 (2002)). The Office acknowledges that Conti-Fine and Lollar do not teach the natural substance is erythropoietin. The Office asserts that Bunn describes a method of deciding to initiate or terminate administration of erythropoietin based on an assessed autoantibody. Office Action at page 9. The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the modified method of Conti-Fine to erythropoietin. *Id.* Applicants respectfully traverse the rejection.

As discussed in detail above, the combination of Conti-Fine and Lollar neither teaches nor suggests the invention as claimed because it fails to disclose altering level or concentration of a therapeutic administration of a natural substance to a subject based on the level of an auto antibody. This deficiency is not solved by the combination with Bunn. Bunn discusses a serious adverse effect of epoetin–red-cell aplasia–because of an immune response to epoetin. *See* Bunn at page 522, left column, third paragraph. Bunn then discusses the mechanism of the formation of anti-erythropoietin antibodies in the patients who developed red-cell aplasia. *See* Bunn at page 522, right column, third paragraph. In contrast to the Office's assertion, Bunn does not teach or suggest a method of deciding to initiate or terminate administration of erythropoietin based on an assessed autoantibody. It does not remedy the deficiencies of Conti-Fine and Lollar as discussed above.

Accordingly, the Office has failed to establish a *prima facie* case of obviousness because combining Conti-Fine, Collar and Bunn does not teach or suggest all limitations of the presently claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Lollar in View of Voller

Claim 31 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lollar in view of Voller (Diagnostic Horizons, Dynasciences Corporation, Published by Microbiological Associates, Vol. 2, No. 1, pages 1-7, 1978). The Office acknowledges that Lollar does not teach the autoantibody is assessed by a sandwich assay format. The Office asserts that Voller teaches that it is known in the art of ELISA assays to provide sandwich assay formats to determine a substance such as antibodies in a sample. Office Action at page 10. The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a sandwich assay format into the method of Lollar. *Id.* Applicants respectfully traverse the rejection.

As discussed in detail above, Lollar neither teaches nor suggests the invention as claimed because Lollar fails to disclose altering level or concentration of a therapeutic administration of a natural substance to a subject based on the level of an auto antibody, and this deficiency is not solved by the combination with Voller.

Accordingly, the Office has failed to establish a *prima facie* case of obviousness because combining Collar and Voller does not teach or suggest all limitations of the presently claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Lollar in View of Stevens

Claims 39 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lollar in view of Stevens (Clinical Immunology and Serology, A Laboratory Perspective, Chapter

10, Labeled Innumoassays, pages 144-146, 1996). The Office acknowledges that Lollar does not teach labeling the natural substance and separating labeled autoantibody complex from the reaction mixture. The Office asserts that Stevens teaches that it is known in the art of immunoassays to label either the ligand or receptor and to provide separation steps to separate reacted complex from unreacted complexes prior to detection of the labeled complexes, and that the labels can be radioactive, enzymes and chemiluminescent labels. Office Action at page 11. The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate labels and separation steps such as taught by Stevens into the method of Lollar. *Id.* The Office further asserts that since the combination of Lollar and Stevens teaches reagents consonant to those instantly claimed, it is deemed the molecular weight of the low molecular weight label that is capable of binding the unhindered natural substance comprises less than about 50%, or the optimum proportion of the molecular weight of the low molecular weight label versus the unhindered natural substance can be determined by routine experimentation and thus is obvious. Office Action at pages 11-12. Applicants traverse the rejection.

Claim 40 has been canceled without prejudice or disclaimer. Therefore, Applicants address this rejection in regard to claim 39 only.

As discussed in detail above, Lollar neither teaches nor suggests the invention as claimed because Lollar fails to disclose altering level or concentration of a therapeutic administration of a natural substance to a subject based on the level of an auto antibody, and this deficiency is not solved by combination with Stevens.

Accordingly, the Office has failed to establish a *prima facie* case of obviousness because combining Collar and Stevens does not teach or suggest all limitations of the presently claimed invention. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532212002000.

Respectfully submitted,

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